

### **REMARKS/ARGUMENTS**

Upon entry of the present amendment, claims 1, 2, 4, 8, 9, 11 and 13-17 are pending in this application. Claims 1, 2, 4, 8, 9 and 11 have been amended and claims 13-17 have been added. Support for the amendment to claim 1 appears at least in claim 7 as filed. Support for new claims 13-17 appears at least in the specification at page 47, lines 1-9.

Claims 3, 5-7, 10 and 12 have been cancelled. Applicants reserve the right to pursue all cancelled subject matter in a continuing application or applications.

The present amendment does not introduce new matter.

### **Claim Objections**

The Examiner has objected to claims 1 and 8 for reciting the punctuation "{...}" and "(...)". As suggested by the Examiner, Applicants have amended claims 1 and 8 to delete "{...}" and "(...)" and to recite the appropriate punctuation numeral ",",.

### **Rejection under 35 U.S.C. §103**

Claims 1, 2, 4, 7, 8, 9 and 11 are rejected under 35 U.S.C. §103, as being unpatentable over U.S. Patent 5,853,703 to Cerami ("Cerami") in view EP 0 458 589 A1 to Kabushiki ("Kabushiki"). The Examiner states that Cerami discloses thiazolium compounds of Formula I (including 3-(2-phenyl-2-oxoethyl)-4,5-dimethylthiazolium bromide) and their use in treating lens proteins susceptible to aging. The Examiner also states that Kabushiki discloses a method of lowering ocular pressure by administering an effective amount of a composition containing a prostaglandin and a cholinergic agent. Thus, the Examiner asserts that it would be obvious to modify the methods of Cerami to additionally include the cholinergic agent of Kabushiki because the skilled artisan would reasonably expect the ocular compositions containing an additional cholinergic agent to reduce any ocular hypertension suffered by the patients in Cerami. See, Office Action pages 3-5. The rejection is traversed to the extent it is applied to the claims as amended.

Claim 1, from which remaining claims subject to the rejection properly depend, has been amended to recite a "method of decreasing intraocular pressure or improving ocular accommodation in an animal, including a human, comprising administering (A) an effective amount of a cholinergic agent; and (B) an effective amount of a compound of the formula I."

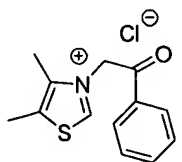
It is well recognized under U.S. law, that any rejection of a claim for obviousness over a combination of prior art references must establish that: (1) the combination produces the claimed invention; (2) the prior art contains a suggestion or motivation to combine the prior art references in such a way as to achieve the claimed invention; and (3) the prior art reveals that in so making or carrying out [the claimed invention], those of ordinary skill would have a reasonable expectation of success. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

Applicants submit that one of ordinary skill in the art would not be motivated to combine the teachings of Cerami and Kabushiki to reach the present invention; and further, Applicants submit that the skilled artisan combining the teachings of Cerami with the teachings of Kabushiki would have no reasonable expectation of success in achieving the claimed invention.

As stated by the Examiner, while Cerami discloses thiazolium compounds of Formula I and various therapeutic uses for these compounds, Cerami does not teach or suggest methods of decreasing intraocular pressure or improving ocular accommodation by combining cholinergic agents and the compounds of Formula I.

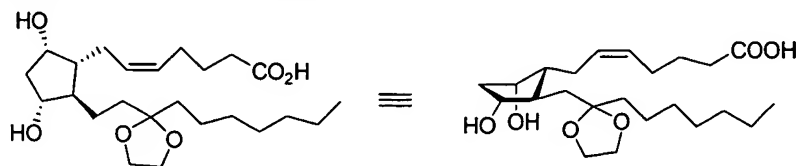
Applicants submit that Kabushiki does not cure the deficiencies of Cerami. Kabushiki merely discloses the combination of a cholinergic agent and a specific prostaglandin compound (13,14-dihydro-15-ketoprostaglandin) to treat ocular hypertension. Kabushiki does not teach or suggest thiazolium compounds. Further, one of ordinary skill in the art would readily recognize that the thiazolium compounds of the instant invention and prostaglandins are structurally distinct and possess very different biological activities.

Thiazoliums are aromatic 5-membered rings, which have the special property of being flat, planar molecules. The thiazolium compounds of the instant invention are heteroaromatic, charged molecules which inhibit the formation of (or reverse) pre-formed advanced glycosylation of proteins (advanced glycosylation end products, AGEs). One example includes 3-(2-phenyl-2-oxoethyl)-4,5-dimethylthiazolium chloride:

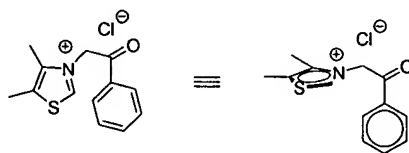


On the other hand, prostaglandins are a well known group of naturally occurring lipid molecules which are derived from fatty acids and present in virtually all tissues and organs. Every prostaglandin contains 20 carbon atoms, including a 5-membered aliphatic carbon ring.

The 5-ring structure of prostaglandins is, however, not planar. For example, the prostaglandin, 13,14-dihydro-15-ketoprostaglandin, of Kabushiki is thought to have the following structure:



whereas the 5-membered ring in the thiazolium compounds of the invention (exemplified below by 3-(2-phenyl-2-oxoethyl)-4,5-dimethyl-thiazolium chloride) has a flat, planar structure:



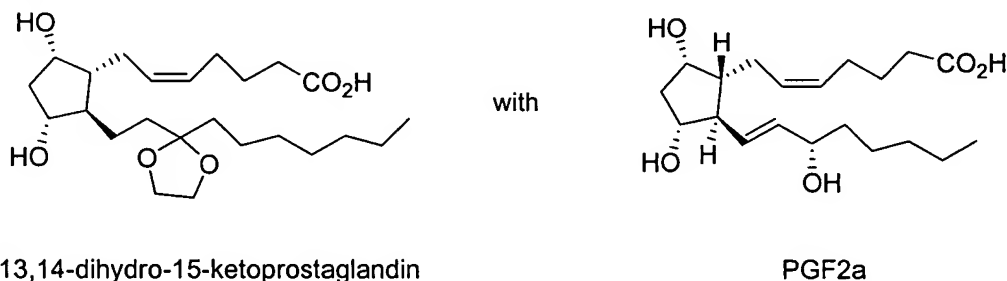
There are currently nine known prostaglandin receptors on various cell types. Prostaglandins act on a variety of cells such as vascular smooth muscle cells causing constriction or dilation, on platelets causing aggregation or disaggregation and on spinal neurons causing pain. Prostaglandins are most commonly known in the art to cause muscular constriction and mediate inflammation. Other known effects of prostaglandins are calcium movement, hormone regulation and cell growth control. Kabushiki does not teach that prostaglandins inhibit the formation of AGE products, nor is it taught in the art that prostaglandins inhibit this process.

Applicants submit that based on the structural and biological differences between the thiazolium compounds Cerami and the prostaglandin family, one of ordinary skill in the art would not be motivated to combine Cerami and Kabushiki. The fact that references can be combined or modified does not render the resulting combination obvious unless the prior art also suggests the desirability of the combination. (See MPEP §2143.01, citing *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990)). As described above, there is no suggestion in either reference that would motivate a skilled artisan to modify the methods to decrease intraocular pressure using a combination of a thiazolium compound of formula I and a cholinergic agent. Thus, the mere fact that the Cerami and Kabushiki references can be combined is not sufficient to establish a *prima facie* case of obviousness.

Moreover, an assertion that modifying the Cerami reference would have been within the ordinary skill of the art at the time the claimed invention was made because the cited references were individually known in the art at the time the instant application was filed is also insufficient to establish a *prima facie* case of obviousness without some objective reason to combine the

references. (See MPEP §2143.01, citing *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pate. App. & Inter. 1993)). Thus, the mere fact that the Cerami and Kabushiki references were known in the art individually at the time the instant application was filed does not render the claimed invention obvious, as there is no teaching or suggestion in the Cerami reference that would motivate one of ordinary skill in the art to modify the methods described therein.

Further, Applicants submit that Kabushiki teaches away from the present invention. Kabushiki teaches that when a cholinergic agent, such as pilocarpine, is combined with other prostaglandins, such as PGF<sub>2</sub>α e.g., not 13,14-dihydro-15-ketoprostaglandin, the subject of the Kabushiki invention), the ocular pressure lowering activity of PGF<sub>2</sub>α is inhibited by the cholinergic agent. See, Kabushiki page 2, lines 29-30. Thus, the skilled artisan reading Kabushiki would readily recognize that the art of combining any prostaglandin with any cholinergic agent is unpredictable: while one specific prostaglandin compound (13,14-dihydro-15-ketoprostaglandin) treats ocular hypertension in combination with a cholinergic agent, other compounds in the prostaglandin family with very similar structures and which are thought to possess similar biological function, are unable to lower ocular pressure and treat ocular hypertension. Compare:



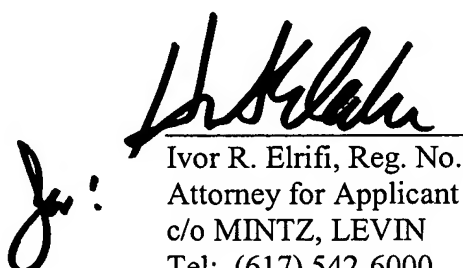
Since thiazolium compounds and prostaglandins are structurally distinct, and because combinations of any and all prostaglandins with cholinergic agents are effective in treating ocular hypertension, Applicants submit that the skilled artisan would have no motivation to combine Cerami and Kabushiki. Further, the skilled artisan would have no reasonable expectation of success combining the methods of using thiazolium compounds of Cerami with the prostaglandin/cholinergic compounds used in the methods of Kabushiki to reach the present invention.

Accordingly, Applicant believes that the Examiner has failed to establish a prima facie case of obviousness, and this rejection should be withdrawn.

### CONCLUSION

On the basis of the foregoing amendment and remarks, Applicants respectfully submit that the pending claims are in condition for allowance and a Notice of Allowance for the pending claims is respectfully requested. If there are any questions regarding this application that can be handled in a phone conference with Applicants' Attorneys, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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